REMARKS

Applicants submit this paper in response to the Office Action dated August 7, 2003 that was issued in the above-identified application.

Claims 1-40 are pending. Claims 1-31 and 34-40 have been withdrawn from consideration. Thus, claims 32 and 33 are currently under consideration.

Claim 32 has been amended as discussed below. The specification has also been amended to correct various informalities. Support for the amendments can be found throughout the specification and claims as originally filed and there is no new matter added as a consequence of the amendments to the claims or the specification.

Restriction Requirement

The Examiner has been unpersuaded by the arguments provided by the Applicant in the response to the restriction requirement and has now deemed the requirement proper and final. Applicants preserve the right to petition the final decision regarding the restriction requirement.

Objections to the Specifications

The Examiner has required the correction of various informalities in the specification. The Examiner has objected to the use of Accession and other reference numbers for sequences disclosed thoughout the specification. The numbers have been deleted as requested by the Examiner.

The reference to Wang et al. at page 34, para 59 is incorrect as noted by the Examiner. The correct citation has been inserted into the specification.

The Examiner has also requested that the specification be checked for minor errors. Various typographical errors have been discovered and corrected herein, as requested.

Objections to the Claims

Claim 33 is objected to as being improper for containing an improper Markush group. The Examiner alleges that each of the cited protein kinases in claim 33 has a specific utility and structure because a compound which occupies one inhibitor binding site would not be expected to bind to a similar site in different protein kinase.

Applicants respectfully traverse. Members of a Markush group must "(1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." (MPEP § 803.02).

Applicants submit that the Markush group recited in claim 33 satisfies both requirements for a Markush group. Each member of the Markush group is a protein kinase that possesses the claimed protein kinase inhibitor binding site. The protein kinase inhibitor binding sites from these proteins share the common structural elements set forth in claim 32, i.e. three-dimensional structural homology to a protein kinase domain starting with linker L5 (residues 78-85) that joins helix C (residues 63-77) with β4 (residues 84-89), the crossover connection (L7) (residues 100-115) and ending at a C-terminus (βL16) (residues 310-336), wherein said domain is described to according to residues of p38, wherein p38 has the amino acid sequence set forth in SEQ ID NO:1. Each member of this group is capable of binding to candidate inhibitors and useful for designing protein kinase inhibitors that do not bind to the ATP binding site of protein kinases (see specification, para 0018, 0023).

Furthermore, the members of the Markush group all have in common, homologous residues from the regions that form the claimed inhibitor binding site. GSK3 and Akt, for example, were identified based on sequence alignments; these proteins have C-terminal tails that are bound to a similar locus as those of the MAP kinases, which are known to possess this site.

Therefore, the members of the Markush group share both a common utility and specific structural features that are essential for their common use. Thus, Applicants submit that the Markush group recited in claim 33 is proper.

35 U.S.C. § 101 Rejection

Claims 32 and 33 have been rejected under 35 U.S.C. § 101 because the invention is allegedly directed to non-statutory subject matter. Specifically, the Examiner alleges that "an inhibitor binding site" is naturally occurring and considered to be non-statutory subject matter. The Examiner has suggested the insertion of the term "isolated" to overcome the rejection. Furthermore, the Examiner has alleged that a claim directed to a property of a protein such as a three dimensional structure or part thereof is not patentable subject matter because they are not a process, machine, manufacture or composition of matter. Applicants respectfully traverse the rejection.

Claim 32 recites an isolated protein kinase inhibitor binding site whose amino acid sequence corresponds to an amino acid sequence of, and has three-dimensional structural homology to a protein kinase domain starting with linker L5 (residues 78-85) that joins helix C (residues 63-77) with β4 (residues 84-89), the crossover connection (L7) (residues 100-115) and ending at a C-terminus (βL16) (residues 310-336), wherein said domain is described according

according to residues of p38, wherein p38 has the amino acid sequence set forth in SEQ ID NO:1. Thus, the claimed inhibitor binding site is limited in having a set of structural features. Such a composition is not naturally occurring, because the site **starts with** linker L5 and includes other structural features of an inhibitor binding site, but **does not encompass** other domains of a protein kinase, in particular an ATP binding site. Therefore, the inhibitor binding site, as claimed, would not exist as an independent entity in nature.

In addition, Applicants submit that claim 32 is not directed to a property of a protein. Claim 32 relates to a molecule having specific structural features that may have a three dimensional structural homology to known proteins. Applicants assert that claim 32 recites a molecule that is far more than a mere intangible property of a known protein.

However to further prosecution of the application, Applicants have inserted the term "isolated" to overcome the rejection, as recommended by the Examiner. Therefore, Applicants request the withdrawal of the rejection under 35 U.S.C. § 101 of claims 32 and 33.

35 U.S.C. §112, ¶2 Rejection

The Examiner has rejected claims 32 and 33 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner alleges that the claim does not clearly set forth the metes and bounds of the invention. The Examiner allegedly finds two meanings to the claim, i.e. a polypeptide comprising residues 78-336 of SEQ ID NO:1 and structure of the protein kinase inhibitor binding site. The Examiner also alleges that the specification does not

disclose atomic coordinates for any protein kinase, including p38, and that the p38 structure is poorly described. Applicants respectfully disagree.

Claim 32 has been amended to more clearly point out and distinctly claim the subject matter which Applicant regards as the invention. As indicated above, claim 32 relates to an isolated protein kinase inhibitor binding site having (1) an amino acid sequence that corresponds to, and (2) a three-dimensional structural homology to a specified protein kinase domain similar to one found in p38. The claimed isolated protein kinase inhibitor binding site comprises a structure having an amino acid sequence corresponding to the amino acid sequence of, and a three dimensional structural homology to, a protein kinase domain starting with linker L5 (residues 78-85) that joins helix C (residues 63-77) with β4 (residues 84-89), the crossover connection (L7) (residues 100-115) and ending at a C-terminus (βL16) (residues 310-336), wherein said domain is described to according to residues of p38, wherein p38 has the amino acid sequence set forth in SEQ ID NO:1. The claimed binding site is not expressly limited to residues 78-336 of SEQ ID NO:1, as alleged by the Examiner. In fact, the atomic coordinates of an entire molecule, such as p38, is not necessary for claiming the present invention. The claimed molecule only relates to the protein kinase domain formed by the aforementioned regions of the p38 molecule. As indicated in the instant specification, this domain may be shared among various other protein kinases (specification, page 16, para 23). Furthermore, the specification provides an alignment of homologous regions of these various protein kinases, showing homologous amino acid residues in Figure 7. Applicants submit that claim 32, as amended, is not indefinite and distinctly claims the subject matter of the invention. Therefore, Applicants

respectfully request withdrawal of the rejection of claims 32 and 33 under 35 U.S.C. § 112, second paragraph.

35 U.S.C. §112, ¶1 Rejection

The Examiner has rejected claim 32 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed had possession of the claimed invention. The Examiner alleges that claim 32 is directed to all possible "protein kinase inhibitor binding sites" and argues that the specification fails to disclose the three dimensional structure of any protein kinase, or any inhibitor binding site. The Examiner alleges that the specification also does not disclose any particular structure to function/activity relationship in the disclosure of p38 bound to an inhibitor. The Examiner states that no atomic coordinates are provided in the specification, and alleges that one of skill in the art would not be able to construct the inhibitor binding site. Therefore, the Examiner alleges that the specification does not sufficiently describe the claimed invention in full, clear, concise and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention. Applicants respectfully traverse.

Applicants submit that the specification clearly demonstrates that the inventors at the time the application was filed had possession of the full scope of the presently claimed invention. An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical

properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Guidelines for Examination of Patent Application Under the 35 U.S.C., ¶1, "Written Description" Requirement.* 66 FR 1099, 1106. Claim 32 clearly recites detailed relevant identifying characteristics, i.e. protein domain structure starting with linker L5 (residues 78-85) that joins helix C (residues 63-77) with β4 (residues 84-89), the crossover connection (L7) (residues 100-115) and ending at a C-terminus (βL16) (residues 310-336), wherein said domain is described according to residues of p38. Not only is the structure clearly set forth in the claim, the specification indicates that this domain structure exhibits the functional characteristic of binding to a protein kinase inhibitor. Therefore, Applicants submit that the specification clearly shows that the inventors had possession of the invention at the time of filing.

The Examiner appears to suggest that the three dimensional structure of the entire p38 molecule is required to show that the inventor had possession of the claimed invention. In response, Applicants submit that the specification clearly provides support for a protein kinase inhibitor binding site having the structural elements from p38, since the specification discloses (1) a method of obtaining the crystal of p38 with inhibitors (sulindac sulfide and PD98059), (2) a method of determining the structure of the protein kinase with inhibitors, (3) determination of the crystal structure of the inhibitor binding domain of p38, and (4) essential inhibitor kinase domain structures, i.e. loops and helices, that correspond to the aforementioned inhibitor binding domain of p38. The structure of the entire p38 molecule is not required to show possession of the claimed inhibitor binding domain. However, Figures 4 and 5 of the specification show ribbon diagrams of the entire structure of p38. In fact, only a determination of the inhibitor binding

domain is of interest, highlighted by Figure 3(a) (sulindac sulfide) and Figure 3(b) (PD98059), and is required to show possession of the claimed invention, i.e. the domain. The structure of the rest of the molecule would not be needed to describe the invention.

Furthermore, the inventors have identified specific, crucial amino acid residues within the inhibitor binding domain, corresponding to amino acids Lys 79, Glu 81, His 107, Lys 165, and the C-terminus, 351-354 of p38, where the inhibitors bind to the domain. (specification, page 16, para 23). Residues that are homologous to those entified in p38 from other protein kinases may also function in a similar manner. Other protein kinases are disclosed in the specification, along with an alignment of the regions from these proteins with the significant amino acids highlighted, demonstrating that this region is shared by these other protein kinases (specification, page 16, para 23; Figure 7). In addition, it is within the knowledge of one of skill in the art to determine the structure of the inhibitor binding domain of these listed protein kinases (specification, 0027-0030; pp 18-20). For this additional reason, Applicants submit that the inventors at the time of the invention had possession of the claimed invention.

In addition, the Examiner alleges that the specification does not enable a person skilled in the art to make and use the scope of the invention commensurate with the claims. The Examiner alleges that the claims are broader than the enablement provided by the disclosure with regard to the inhibitor binding site of any protein kinase. The Examiner indicates that the specification does not disclose additional representative species of the protein kinase inhibitor binding sites by identifying structural characteristics or properties other than the structural element in claim 32. The Examiner acknowledges that the specification provides guidance regarding crystallization of p38 with two inhibitors, but alleges that the specification lacks knowledge regarding all protein

kinases from any biological source which may have an inhibitor binding site and their three dimensional structure. The Examiner asserts that searching for a protein kinase having an inhibitor binding site with the structural element of claim 32 is outside of the realm of routine experimentation and predictability of success is low. In the absence of guidance, i.e. biological source of protein kinase/inhibitor binding site and crystallization conditions to obtain an adequate crystal suitable for structure determination, the Examiner alleges that the experimentation left to those skilled in the art is undue. Applicants respectfully disagree.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *In re Wands*, 858 F2d. 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir 1988). Applicants assert that the claimed invention can be carried out without undue experimentation. First of all, the specification clearly teaches a sufficient number of representative examples of the protein kinase inhibitor binding sites. In fact, the specification identifies seven protein kinases that exhibit the protein kinase inhibitor binding domain of the present invention, i.e. IKK-β, Map/ERK kinase, JNK, MEK, GSK-3, Akt, and NIK. Furthermore, Figure 7 shows an alignment of the corresponding regions from these protein kinases with p38 and, as indicated above, crucial residues within these regions. The alignment shows the presence of similar homologous residues in the regions of these sequences, providing guidance for one of skill in the art to identify similar regions having these crucial residues.

Secondly, it is clearly within the skill set of a structural biologist to identify protein kinases having an inhibitor binding site with the structural elements recited in claim 32. An alignment of various candidate protein kinases can be readily performed as shown in Figure 7.

The Examiner is incorrect in requiring the information regarding *all* protein kinases from *any* biological source which may have an inhibitor binding site and their three dimensional structure. Practice of the invention does not involve the unguided screening of vast numbers of biological source for a desired protein kinase or crystallization conditions of these proteins for a desired protein kinase inhibitor binding site that is unpredictable, as alleged by the Examiner. The skilled artisan can use the information provided in the specification to identify other kinases. Screening for protein kinases having the structural elements recited in claim 32 would involve an alignment of potential candidates for residues homologous to ones identified in Figure 7. Such an analysis is within the realm of routine experimentation and certainly within the knowledge of a skilled artisan at the time of the invention. Determination of the structure of the inhibitor binding domain of potential protein kinases having the similar conserved residues is also within the knowledge of the skilled artisan (specification, para 0027-0030; pp 18-20). Applicants submit that the specification provides sufficient disclosure and guidance, supplemented by knowledge of one reasonably skilled in the art, for the skilled artisan to make and use the claimed invention without undue experimentation.

For the foregoing reasons, Applicants respectfully request withdrawal of the rejection of claims 32 and 33 under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 102 Rejections

Claims 32 and 33 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Wilson et al. The Examiner alleges that Wilson et al. teaches a human p38α having the amino acid sequence disclosed in the specification in Figure 1 and the three dimensional structure of

human p38α. The Examiner acknowledges that Wilson et al. does not teach the p38 inhibitor binding site of claim 32, but alleges that the inhibitor binding site is inherent. The Examiner also cites the atomic coordinates of the structure which have been deposited in the protein data bank at Brookhaven National Laboratory.

Claims 32 and 33 have also been rejected under 35 U.S.C. § 102(e) as being anticipated by Bellon et al. (US 6,387,641). The Examiner alleges that Bellon et al. teach human phosphorylated p38γ of SEQ ID NO:1 and the three dimensional structure. The Examiner acknowledges that Bellon et al. does not teach the p38 inhibitor binding site of claim 32, but alleges that the inhibitor binding site is inherent. The Examiner also cites the atomic coordinates of human phosphorylated p38γ taught by Bellon et al.

In relying upon the theory of relevancy, the examiner must provide a basis in and/or technical reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990). The present invention relates to an isolated protein kinase inhibitor binding site whose amino acid sequence corresponds to an amino acid sequence of, and has three-dimensional structural homology to, a protein kinase domain starting with linker L5 (residues 78-85) that joins helix C (residues 63-77) with β4 (residues 84-89), the crossover connection (L7) (residues 100-115) and ending at a C-terminus (βL16) (residues 310-336), wherein said domain is described to according to residues of p38, wherein p38 has the amino acid sequence as set forth in SEQ ID NO:1. The Examiner has failed to show that the three dimensional structure of p38, as a whole, as taught by either Wilson et al. or Bellon et al. would apprise one of skill in the art of the inhibitor binding site as presently claimed.

Wilson et al. teach the crystal structure of unphosphorylated p38 and that the structure may be used to identify inhibitors of p38. However, there is no description of the inhibitor binding domain of the present invention. Wilson et al. is concerned with the ATP binding domain and the phosphorylation site as candidates for inhibitor domain binding. There is no disclosure of the inhibitor binding region identified in the present invention or the present teaching to look to a domain other than the ATP binding and phosphorylation sites as potential domains to identify inhibitors.

Bellon et al. teaches the crystal structure of phosphorylated p38γ and that the structure may be used to design and identify inhibitors of p38γ. However, Bellon et al. is primarily directed to the ATP binding domain of the protein, since the crystallized structure of phosphorylated p38γ is complexed with a non-hydrolyzable ATP analog. There is no discussion of the inhibitor binding domain identified in the present invention as a candidate inhibitor binding region. Bellon et al. point out the "hinge" region of p38γ, which is in the vicinity of the inhibitor binding domain of the present invention. In a comparison of the phosphorylated and unphosphorylated forms of p38γ, Bellon et al. teaches that the difference in the two structures is mediated through movement of the domains of the proteins centered around the hinge region. (col. 25, lines 32-47; col. 26, line 64 to col. 27, line 4). However, there is no suggestion or motivation provided that this region may be a domain subject to inhibitor binding.

In fact, the specification clearly discloses that the inhibitor binding domain as recited in claim 32 is outside of the ATP binding domain and does not compete with the ATP binding domain. In further support of the claimed invention, Applicants present a comparison of the structure of p38 in complex with sulindac sulfide (present invention) and p38 in complex with a

non-hydrolyzable ATP analog, ANP-PNP (as in Bellon et al.) (attached as Exhibit 1). Exhibit 1 also shows the binding of another inhibitor, SB203580, to the ATP binding domain (Exhibit 1, middle). The inhibitor binding domain of the present invention is in the hinge region, i.e. on the upper left portion of the ribbon diagram shown in Exhibit 1, whereas the ATP binding domain is located centrally. Exhibit 2 shows the superimposition of the three structures to distinguish the differences in the inhibitor binding domains in each structure.

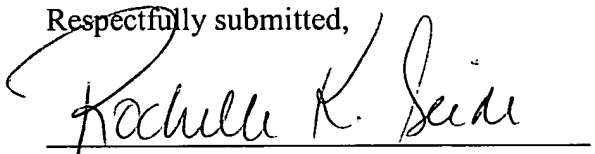
For the foregoing reasons, Applicants submit that the Examiner has failed to show that the inhibitor binding domain of the present invention necessarily flows from the cited references. Therefore, Applicants submit that neither Bellon et al. nor Wilson et al. anticipate the presently claimed invention and respectfully request the withdrawal of the rejection of claims 32 and 33 under 35 U.S.C. § 102.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the outstanding rejections and allowance of the pending claims.

Applicants request three a month extension of time and enclose herewith the requisite fee as set forth in 37 C.F.R. § 1.17(a)(3). Applicants do not believe that any additional fee is required in connection with the submission of this document. However, should any fee be required, or if any overpayment has been made, the Commissioner is hereby authorized to charge any fees, or credit or any overpayments made, to Deposit Account 02-4377. A duplicate copy of this sheet is enclosed.

Respectfully submitted,



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